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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Robert E. Garfield et al. Examiner: H. Lilling

Serial No.: 09/121,849 Group Art Unit: 1651

Filed: July 24, 1998

Title: TREATMENT OF PREECLAMPSIA TOXEMIA AND PRETERM LABOR WITH COMBINATION OF PROGESTATIONAL AGENT AND A NITRIC OXIDE SYNTHASE SUBSTRATE AND/OR DONOR

#26
4/11/02

BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

Sir:

This is an appeal from the decision of the Examiner finally rejecting claims 14, 17-19 and 29 of the above-identified application.

(1) REAL PARTY IN INTEREST

The application is assigned of record to Schering Aktiengesellschaft and The Board of Regents, University of Texas System, who are the real parties in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected: 14, 17, 18, 19 and 29

Claims allowed: none

Claims canceled: 28 and 31

Claims withdrawn: 1-13, 15, 16, 20-27, 30, 32 and 33-35

Claims on Appeal: 14, 17, 18, 19 and 29. A copy of claims on appeal is in the attached Appendix.

(4) STATUS OF AMENDMENTS AFTER FINAL

No amendments after the Final Rejection have been proposed by Appellants

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a novel pharmaceutical comprising three ingredients: (a) a progestin; (b) a nitric oxide synthesis substrate, a nitric oxide donor or both, and (c) at least one of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing PGI_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-mimetic activities, and a TXA_2-antagonist, in amounts effective to ameliorate the symptoms of preeclampsia accompanied or unaccompanied by preterm labor in a pregnant female mammal, dysmenorrhea, or functional uterine bleeding or hemorrhaging. See, *e.g.*, the Abstract and the specification at page 2, lines 10-21 and page 14, lines 3-9. For the purposes of examination, the following species of the above genera were selected: (a) the progestin, progesterone; (b) the NO donor, nitroglycerine; (c) the cyclooxygenase inhibitor, aspirin.

As noted above, this pharmaceutical composition is useful for treating, *e.g.*, preeclampsia accompanied or unaccompanied by preterm labor in a pregnant female mammal, dysmenorrhea, or functional uterine bleeding or hemorrhaging.

(6) ISSUES

The only issue on appeal is whether claims 14, 17, 18, 19 and 29 are patentable under 35 U.S.C. §103.

(7) GROUPING OF THE CLAIMS

All of the claims on appeal are grouped together.

(8) APPELLANTS' ARGUMENTS

The claims on appeal have been rejected under 35 U.S.C. §103 over Harrison *et al.* USP 5,508,045 ("Harrison").

This rejection is unwarranted. Harrison does not disclose or suggest a pharmaceutical composition comprising, *e.g.*,

a progestin (compound (a)),

a nitric acid substrate or donor (compound (b)), **and**

at least one of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing PGI_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGl_2-mimetic activities, or a TXA_2-antagonist (compound (c)).

At best, Harrison discloses a composition which comprises a nitric oxide substrate or donor (applicants' component (b)) and the **optional** presence of other agents. There is no disclosure or suggestion motivating a composition comprising the **three** specific types of agents of the instant claims.

Harrison discloses a laundry list of optional agents that can be present, in addition to applicants' component (b), in its composition. These optional agents include, *e.g.*, the generic categories of "other tocolytic agents, analgesics, [and] vasopressors" (col. 20, lines

57-59). This is not the ternary combination recited in applicants' claims.

Among the wide variety of tocolytic agents listed are "β-adrenergic agonists, oxytocin antagonists, prostaglandin synthesis inhibitors such as prostaglandin synthase inhibitors, magnesium salts, calcium transport blockers, ethanol, phosphodiesterase inhibitors and progestins, among others" (col. 21, lines 26-31), or oxytocyn antagonists (col. 22, lines 28-31). Within these broad categories of tocolytic agents, Harrison further lists, *e.g.*, as β-adrenergic agonists, epinephrin, isoproterenol, isopropylnorepinephrine, p-hydroxyphenylisopropylarterenol, isoxsuprine, orciprenaline, (1-(3,5-dihydroxyphenyl)-2-isopropylaminoethanol sulphate, salbutamol, terbutaline, analogues thereof, and other agents known in the art (col. 21, lines 45-50); as prostaglandin synthesis inhibitors, indomethacin, naproxen, aspirin, meclofenamic acid, phenylbutazone, analogues thereof and other agents (col. 21, lines 54-58); as calcium transport blockers, nicardipine, nitrendipine, nifedipine, analogues, and other agents known in the art (col. 22, lines 5-8); and as phosphodiesterase inhibitors, papaverine, aminophylline, cilostamide, valeramide, zaprinist, rolipram, amrinone, dipyridamole, theophylline, analoges thereof, and other agents known in the art.

Among the analgesics listed are acetaminophen, acetylsalicylic acid, morphine, fentanyl or other similar acting agents known in the art (col. 22, lines 39-42). Among the vasopressors listed are ephedrine, norepinephrine, dopamine and epinephrine, analogues thereof, and other similar acting agents known in the art (col. 22, 48-51).

Thus, it is clear that Harrison suggests very generically an infinite set of possible combinations. Such a broad statement does not render obvious any particularly subsumed combination of specific compounds which may happen to satisfy the recitations of the claims here. Without more, there can be no motivation to make the selections leading to the claimed invention. See, *In re Baird*, 29 USPQ2d 1550 (Fed. Cir. 1994).

But, if one looks to the specification and examples in Harrison for guidance as to which components to select from the infinite laundry list of optional agents that can be included in Harrison's compositions in addition to an NO source, one is not led to select the instantly claimed composition; rather, all teachings are away.

The specification teaches (*e.g.*, at col. 23, lines 18-28) that a particularly preferred embodiment of the invention is an NO compound such as L-arginine (or a precursor or analog thereof) and a phosphodiesterase inhibitor such as papaverine or zaprinast (see, especially col. 23, lines 26-28). Phosphodiesterase inhibitors are not among the components of the instantly claimed composition. Furthermore, none of the examples discloses the use of a nitric oxide source (*i.e.*, a nitric acid substrate or donor) plus a progestin (appellants' compound (a)), let alone the use of a combination of all three of the components recited in the instant claims. Therefore, if anything, Harrison teaches away from the instantly claimed composition.

The Examiner argued in the final Office Action of Sept. 13, 2001 that the "exceptionally broad pertinent disclosure [of Harrison] ... would motivate one of ordinary skill to employ the [recited] combinations with a reasonable expectation of success..." However, it is the very "broadness" of Harrison's disclosure which mitigates *against* motivation for one of skill in the art to select the particular combination of three components recited in the instant claims from the laundry list of that exceptionally broad disclosure. *Baird.*

Thus, Harrison discloses three different categories of agents that can be used in addition to an NO donor; each of these categories is essentially infinite in scope. Harrison provides no general guidance (motivation) to select the particular components (a) and (c) for combinations with (b) as recited in the instant claims from the myriad of compounds disclosed in Harrison. Absent such guidance, the reference does not render the claimed invention obvious. *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Baird*, 29 USPQ2d

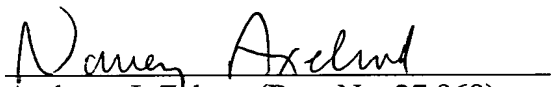
1550 (Fed. Cir. 1994).

Neither Harrison nor what was known to one of skill in the art would have provided motivation to modify Harrison's composition to arrive at applicants' claimed composition. That is, there was no motivation to achieve a composition which includes, in addition to compound (b), both compounds (a) and (c). Absent such motivation, with the requisite reasonable expectation of success, the reference does not render obvious the claimed invention. *In re Vaeck*, 20 USPQ 1438 (Fed. Cir. 1991).

(9) CONCLUSION

For all of the above reasons, it is urged that the decision of the Examiner rejecting claims 14, 17, 18, 19 and 29, on appeal, is in error and should be reversed.

Respectfully submitted,



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APPENDIX

14. (Four Times Amended) A pharmaceutical composition comprising an admixture of effective amounts of:

(a) a progestin and

(b) a nitric oxide synthesis substrate, a nitric oxide donor or both, and,

(c) at least one of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing PGI_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-mimetic activities, and a TXA_2-antagonist, in amounts effective to ameliorate the symptoms of preeclampsia accompanied or unaccompanied by preterm labor in a pregnant female mammal, dysmenorrhea, or functional uterine bleeding or hemorrhaging.

17. The composition according to claim 14, wherein (b) is a nitric oxide donor.

18. (Amended) The composition according to claim 17, wherein the nitric oxide donor is sodium nitroprusside, nitroglycerin, glyceryltrinitrate, SIN-1, isosorbidmononitrate or isosorbiddinitrate.

19. The composition according to claim 17, which comprises a cyclooxygenase inhibitor.

29. A composition of claim 14, wherein the amount of progestin is bioequivalent to 50-300 mg of injected progesterone.